inside blood commentary

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Dombret et al, page 291

Azacitidine in AML: a treatment option?

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In this issue of *Blood*, Dombret et al[1] report the final analysis of the international phase 3 study of azacitidine vs conventional care regimens in older (≥65 years), newly diagnosed acute myeloid leukemia (AML) patients with >30% bone marrow blasts and white blood cell (WBC) counts ≤15 × 10^9/L (AZA-AML-001 study).

The optimal treatment for older AML patients in daily clinical practice remains challenging and is dependent on patient characteristics (age, performance, comorbidity), disease characteristics (cytogenetic and molecular abnormalities, WBC count), and the wishes of the patient.[2] Regular treatment options include best supportive care (BSC) (hydroxyurea, transfusions, antibiotics), low-dose cytarabine (ara-c) (LDAC), and intensive chemotherapy (IC) (anthracycline combined with ara-c, known as "3+7"). Few prospective randomized studies of older AML patients are available to guide these treatment decisions. A small but pivotal clinical trial (n = 60) showed that standard IC decreases early death rates and significantly improves long-term survival, although it is still very poor, compared with BSC.[3] Studies on LDAC and gemtuzumab ozogamicin (GO) reported superior overall survival (OS) compared with BSC, although neither had an effect in patients with adverse cytogenetics.[4,5]

In addition to IC and LDAC, the armamentarium for the treatment of AML has expanded in recent years with 2 cytosine analogs with DNA-hypomethylating properties (also known as hypomethylating agents [HMAs]): azacitidine and decitabine. A post hoc analysis of the prospective AZA-MDS-001 trial for older patients who met the World Health Organization criteria for AML (ie, 20%-30% bone marrow blasts) showed an 18% complete remission (CR) rate, with a survival benefit in favor of azacitidine compared with physicians' choice conventional care regimen (CCR).[6] A recent prospective trial compared decitabine (20 mg/m^2, days 1-5) (n = 242) with physicians' choice CCR (ie, BSC [n = 28]; LDAC [n = 215]) in older, newly diagnosed AML patients with poor- or intermediate-risk cytogenetics.[7] Although the planned primary analysis of this trial after 396 deaths did not show significant improvement of OS with decitabine vs CCR (median OS, 7.7 vs 5.0 months), an unplanned analysis after 446 deaths showed a significant benefit for decitabine. Based on this study, decitabine is now registered for the treatment of AML in Europe.

In the AZA-AML-001 study, older AML patients with newly diagnosed or secondary AML with >30% bone marrow blasts and WBC counts ≤15 × 10^9/L (prior hydroxyurea allowed) were preselected to receive 1 of 3 physicians' choice CCRs. Patients were randomized to receive either azacitidine (75 mg/m^2, days 1-7) (n = 241) or their preselected treatment BSC (n = 45), or LDAC (n = 158), or IC (n = 44). Median OS, the primary end point of the study, was 10.4 months for patients receiving azacitidine compared with 6.5 months for patients receiving CCR, which did not reach statistical significance (hazard ratio [HR] = 0.85 [95% confidence interval (CI), 0.69 - 1.03]; P = .1009). However, patients with poor-risk cytogenetics (HR = 0.68) and those with AML with myelodysplasia-related changes (HR = 0.69) benefited significantly from azacitidine. A prespecified sensitivity analysis for OS that censored patients at the start of subsequent AML therapy showed a longer median OS in patients receiving azacitidine (median 12.1 months) compared with patients receiving CCR (median 6.9 months) (HR = 0.76 [95% CI, 0.60-0.96]; P = .019). Subgroup analyses comparing azacitidine with the various physicians' choice CCRs are reported, although the study was not designed to have sufficient power to demonstrate differences between the individual choices made. The OS of patients treated with azacitidine or LDAC (n = 154 vs 158) did not differ significantly. In this context, it should be noted that in a French prospective

Treatment strategies and outcome in older (>65 y) AML patients

	BSC	LDAC	GO	Intensive chemotherapy	HMAs: Azacitidine (7 d) Decitabine (5 d)
CR (%)	0	15-20	15-20	50-55	15-20
Median OS (mo)	2	4	4-5	10	7-10
5-y OS (%)	0	0	?	10	Not curative, unless consolidated with allo-HCT
Effect in adverse karyotypes		No	No	Limited	Moderate

allo-HCT: allogeneic hematopoietic cell transplantation.

study, IC also did not show superior OS in older AML patients compared with LDAC, despite a higher number of CRs after IC.[8] The observation in the AZA-AML-001 study that azacitidine (n = 43) and IC (n = 44) resulted in comparable survival rates in patients preselected for IC is in the same line, although the number of patients is low. This suggests that patients who are not candidates for IC for various reasons might benefit from treatment with azacitidine. Clearly, prospective randomized studies comparing azacitidine (or decitabine) with LDAC and IC in older unfit and fit AML patients are needed.

Although the primary end point of this study, superior OS, was not met, and limitations in the design of the study hampered the power to detect differences in the preselected treatment options, we can learn many things from the large randomized AZA-AML-001 study. First, post hoc analysis of the patients preselected to BSC demonstrates that azacitidine is superior to BSC. This confirms that active treatment should be considered in all older AML patients. Indeed, considering the results of LDAC previously reported by the MRC group, BSC should probably not have been a preselected option in the design of this trial. Second, this study shows that azacitidine is effective in the subgroup of older patients with adverse cytogenetics. This is an important difference with LDAC and gemtuzumab ozogamicin. Third, this study confirms the clinical observation that azacitidine can have meaningful clinical activity (eg, transfusion independency) and improve survival, even though no CR is achieved. Median OS for patients who did not attain CR was significantly better for patients who received azacitidine compared with CCR (6.9 months vs 4.2 months). Finally, when patients were censored at the start of subsequent AML therapy, the significant longer median OS for those receiving azacitidine compared with CCR suggests that the sequence of treatments is important. Apparently, patients who start with azacitidine are less responsive to rescue treatments than patients who start with LDAC or IC.

Unfortunately, this study did not include extensive biomarker analyses and geriatric assessments to determine the optimal relationship between the various treatments with disease (eg, genotype) and patient-related factors (eg, comorbidity, geriatric assessments).

The AZA-AML-001 study shows that azacitidine has clear activity in AML, particularly in patients with unfavorable cytogenetics or myelodysplasia-related changes. Although azacitidine did not result in a significantly better OS compared with LDAC or IC, this study confirms that, essentially, the majority of older patients should be considered for specific chemotherapy. Because the outcome of treatment of older AML patients is still very poor, additional research is needed (see table). In the perspective of HMAs, this could imply research to improve treatment schedules of HMAs—analogous to what has been pioneered with the 10-day decitabine schedule[9]—to integrate allogeneic hematopoietic cell transplantation in treatment strategies with HMAs, and to identify effective combinations of HMAs and new drugs with activity against AML.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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mTOR inhibition in T-cell lymphoma: a path(way) forward

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In this issue of *Blood*, Witzig et al report on the promising in vitro and in vivo activity of everolimus in T-cell lymphoma (TCL) and pave the way for future combination studies.[1]

The peripheral TCLs are heterogeneous diseases typically associated with unfavorable prognosis and limited treatment options. Standard frontline therapies, such as cyclophosphamide, hydroxydaunorubicin, Oncovin (vincristine), and prednisone (CHOP), produce low rates of cure. Outside of brentuximab vedotin for anaplastic large cell lymphoma, the approved drugs for relapsed disease, pralatrexate, romidepsin, and belinostat, are associated with response rates ranging from 25% to 29% and produce intermediate or long-term benefit for only a minority of patients.[2-5] With an overall